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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER	
HOLT, ANDRIAE M	

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4133	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,032	KOHANE ET AL.	
	Examiner	Art Unit	
	Andriae M. Holt	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *1-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/12/2004 and 5/19/2004*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *9/26/2007* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-20, drawn to a method of treating a neurological disorder, classified in class 604, subclass 19.

II. Claims 21-27, drawn to a method of treating cardiac arrhythmia, classified in class 514, subclass 821.

III. Claims 28-34, drawn to a method of treating preterm labor, classified in class 514, subclass 935.

IV. Claims 35-43, drawn to a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue, classified in class 514, subclass 535; class 514, subclass 179 or other classes depending on the pharmaceutical composition chosen.

Inventions (IV) and (I-III) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the product as claimed can be used in a materially different process of using that product. The product as claimed can be used as an oral pain reliever, to treat allergies and inflammation and as a toxin.

Inventions I, II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are related to methods of treating three unrelated disorders, neurological, cardiac and pre-term labor.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art due to their recognized divergent subject matter and different classification status, restriction for examination purposes as indicated is proper.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product

claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

This application contains claims directed to the following patentably distinct species: pharmaceutical agents. The species are independent or distinct because the agents belong to different drug classes.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 7,10,21,25, 30, 33, 35 and 43 are generic. A responsive election will elect a single pharmaceutical agent for each drug class, site 1 sodium channel blocker, a local anesthetic and a glucocorticoid receptor agonist.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions

unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103 (a) of the other invention.

During a telephone conversation with C. Hunter Baker on September 26, 2007, a provisional election was made without traverse to prosecute the invention of Group IV, claims 35-43. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-34 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. An election of species for the specific pharmaceutical agents was made: site 1 sodium channel blocker is tetrodotoxin, local anesthetic, bupivacaine, and glucocorticoid receptor agonist, dexamethasone.

Claims 1-43 are pending in this application. Claims 1-34 have been cancelled. Claims 35-43 will be examined on the merits.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) is acknowledged. Benefit of US Provisional Application 60/430,240 filed December 2, 2002 is acknowledged.

Information Disclosure Statement

Receipt of Information Disclosure Statements filed on April 12, 2004 and May 19, 2004 is acknowledged.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 43 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 8 of U.S. Patent No. 6,326,020. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are to a composition consisting of a site 1 sodium channel blocker in combination with an agent selected from the group consisting of glucocorticoids. Claims 1 and 8 of US Patent No. 6,326,020 do not claim the local anesthetics, however, it would be obvious to use local anesthetics in combination with site 1 sodium channel blockers, as it is taught by US Patent No. 6,326,020, col. 2, lines 27-40 to enhance the duration of block. The reference teaches the combination of site 1

sodium channel blockers, such as tetrodotoxin, with other agents to give long duration block with improved features, including safety and specificity. US Patent No. 6,326,020 teaches the duration of block is greatly prolonged by combining a toxin with a local anesthetic, vasoconstrictor, glucocorticoid and/or adrenergic drugs.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-43 are rejected under 35 U.S.C. 102(e) as being anticipated by Kohane et al. (US 6,326,020).

Applicant claims a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue comprising a site 1 sodium channel blocker, a local anesthetic and a glucocorticoid receptor agonist. The electrically excitable tissue includes brain, heart and uterine tissue.

Kohane et al. disclose combinations of naturally occurring site 1 sodium channel blockers (claims 35, 39 and 43, site 1 sodium channel blockers, instant invention), such as tetrodotoxin (TTX) (claim 39, tetrodotoxin, instant invention), saxitoxin, decarbamoyl saxitoxin and neosaxitoxin with other agents to give long duration block with improved features, including safety and specificity (col. 2, lines 30-35). Kohane et al. disclose in

one embodiment, duration of block is greatly prolonged by combining a toxin with a local anesthetic and glucocorticoid (col. 2, lines 36-38)(claims 35, 39-41 and 43, site 1, sodium channel blocker, tetrodotoxin, local anesthetic and glucocorticoid, instant invention). Kohane et al. further disclose that bupivacaine is the preferred local anesthetic (col. 7, lines 21-22) (claim 40, bupivacaine, instant invention). Kohane et al. disclose corticosteroids that are useful to prolong in vivo nerve blockade include glucocorticoids such as dexamethasone (col. 7, lines 1-2) (claims 40 and 42, dexamethasone, instant invention). Kohane et al. further disclose in example 5, col. 20, lines 26-52, the combination of tetrodotoxin with bupivacaine and epinephrine with 0.2% dexamethasone (claims 35 and 39-43, tetrodotoxin, bupivacaine and dexamethasone in combination, instant invention). Kohane et al. disclose the combination of tetrodotoxin with bupivacaine provides blockade with durations of about 10 hours and the addition of dexamethasone can produce blockade in excess of 30 hours (col. 20, lines 38-52). A combination of tetrodotoxin, bupivacaine and dexamethasone is taught at col. 4, lines 20-25. The claimed "tissue" is not part of the claimed composition; it is intended use.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (US 6,326,020) in view of Levin (US 2002/00101094).

Applicant's Invention

Applicant claims a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue comprising a site 1 sodium channel blocker, a local anesthetic and a glucocorticoid receptor agonist. The electrically excitable tissue includes brain, heart and uterine tissue.

Determination of the scope of the content of the prior art

(MPEP 2141.01)

The teachings of Kohane et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed above. Kohane et al. also teach that bupivacaine is a particularly long acting and potent local anesthetic when incorporated into a polymer. Kohane et al. teach that its other advantages include

sufficient sensory anesthesia without significant motor blockage, lower toxicity and wide availability (col. 7, lines 24-28).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Kohane et al. do not explicitly teach that the electrically excitable tissue is brain tissue. It is for this reason Levin is joined.

Levin teaches pharmaceutical compositions useful for inhibiting a cerebral neurovascular disorder or a muscular headache in a patient (page 6, paragraph 64). Levin teaches that cerebral neurovascular disorders may be selected from the group consisting of cerebrovascular spasm, seizure, and a neurovascular headache (page 5, paragraph 59)(claim 36, brain tissue, instant invention). Levin teaches the long acting anesthetic pharmaceutical composition comprises a pharmaceutically acceptable carrier and at least one local anesthetic ingredient selected from the group consisting of a long-acting local anesthetic, a persistent local anesthetic and a sustained release formulation of a local anesthetic (page 6, paragraph 60). Levin further teaches in claim 5, page 32, the local anesthetic is bupivacaine (claims 35, 40 and 43, local anesthetic, bupivacaine, instant invention). Levin teaches in an alternate embodiment the long acting local anesthetic pharmaceutical composition further comprises a pharmaceutically active agent such as tetrodotoxin and a glucocorticoid compound (page 6, paragraph 61) (claims 35, 39-43, tetrodotoxin, local anesthetic and glucocorticoid receptor agonist).

Finding a prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kohane et al. and Levin to produce a pharmaceutical composition that would be effective in treating a disorder that affects brain tissue. As taught by Kohane et al. the combination of tetrodotoxin, bupivacaine and dexamethasone produced a safe, specific, and potent composition for intercostal blockade for thoracic post-therapeutic neuralgia, lumbar sympathetic blockade and modality-selective blockade for epidural infusion for postoperative pain. It is known in the art that nerve tissue is electrically excitable tissue. Levin teaches that a local anesthetic composition alone or in combination with tetrodotoxin or a glucocorticoid compound is effective in treating cerebral neurovascular disorders. Thus, as the compositions safely and effectively treat disorders of electrically excitable tissues, one skilled in the art at the time of invention would have been motivated to combine the teachings.

Claims 35-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (US 6,326,020) in view of Webb et al. (US 2001/002404).

Applicant's Invention

Applicant claims a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue comprising a site 1 sodium channel blocker, a local

anesthetic and a glucocorticoid receptor agonist. The electrically excitable tissue includes brain, heart and uterine tissue.

Determination of the scope of the content of the prior art

(MPEP 2141.01)

The teachings of Kohane et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed above.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Kohane et al. do not teach the electrically excitable tissue being heart and uterine tissue. It is for this reason Webb is joined.

Webb et al. teach that conjugates of pharmaceutical agents and a highly lipophilic group, a C8-C26, naturally occurring unbranched carbon chain, have a different selectivity relative to the unconjugated pharmaceutical agents (page 2, paragraph 19). Webb et al. teach in one embodiment, the conjugates render the activity of these conjugates selective for colon tissue, breast tissue and central nervous system tissue (page 2, paragraph 20) (claim 36, brain tissue (nervous system), instant invention). Webb et al. teach that a method is provided for targeting a therapeutic agent to noncentral nervous system tissue to treat a noncentral nervous system condition (page 2, paragraph 21). Webb et al. further teach the noncentral nervous system tissue can be tissue from the cardiovascular system including heart and vascular system (claim 37, heart tissue, instant invention) and reproductive system including uterus

(claim 38, uterine tissue, instant invention) (page 2, paragraph 21-page 3 paragraph 21). Webb et al. teach that the pharmaceutical agent may be any pharmacological compound or diagnostic agent (page 3, paragraph 24). Webb et al. further teach that anesthetic agents include bupivacaine (page 12, paragraph 105)(claim 40, local anesthetic, bupivacaine, instant invention). Webb et al. also teach that glucocorticoid agents include dexamethasone (page 21, paragraph 212)(claims 41-42, glucocorticoid receptor, dexamethasone).

Finding a prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kohane et al. and Webb et al. to produce a pharmaceutical composition that would be effective in treating a disorder that affects brain, heart and uterine tissue. As taught by Kohane et al., the combination of tetrodotoxin, bupivacaine and dexamethasone produced a safe, specific, and potent composition for intercostal blockade for thoracic post-therapeutic neuralgia, lumbar sympathetic blockade and modality-selective blockade for epidural infusion for postoperative pain. Webb et al. teach that the combination of a pharmaceutical agent with a fatty acid provides a method for selectively targeting pharmaceutical agents to desired tissues. Agents claimed in the instant invention are sited. One skilled in the art the time of invention would have been motivated to combine the teachings to produce a pharmaceutical

agent that is effective, highly selective and safe in treating disorders of the heart, brain and uterus.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Kao et al. US Patent No. 5,504,116 and Deitmer et al. "The Intracellular Sodium Activity of Sheep Heart Purkinje Fibres: Effects of Local Anaesthetics and Tetrodotoxin, Journal of Physiology, (1980), Volume 300, pages 269-282.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andriae M. Holt whose telephone number is 571-272-9328. The examiner can normally be reached on 9:00 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Andriae M. Holt
Patent Examiner

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER